

April 26, 2010

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Re: International Formula Council
written comments on the peer review of
the Draft NTP Brief on Soy Infant
Formula

Dear Dr. White:

The International Formula Council (IFC) appreciates the opportunity provided by the National Toxicology Program's (NTP) Board of Scientific Counselors (BSC) to comment on the NTP – Center for the Evaluation of Risks to Human Reproduction (CERHR) Draft Brief on Soy Infant Formula dated March 16, 2010 (DB). The IFC is an association of manufacturers and marketers of formulated nutritional products, e.g., infant formulas (including soy protein-based infant formulas) and adult nutritionals, whose members are based predominantly in North America.*

IFC would like to make the following observations and comments on the NTP-Draft Brief on Soy Infant Formula (DB).

As manufacturers of infant formula, we understand that our products often provide sole source nutrition at a critical time for growth and development. Thus, we continually work to assure our formulas are safe and of the utmost quality. Through ongoing clinical research and routine review and evaluation of the scientific literature, we also work to assure that our products reflect the latest nutrition advances. Infant formula is one of the most highly regulated food products in the U.S. And we take very seriously all issues related to the safety and suitability of our products.

It is from this perspective that we once again bring forward our concerns expressed in comments dated June 11, 2004, March 1, 2006, June 30, 2006, and December 8, 2006 made during the 2006 NTP-CERHR investigation of the safety of soy formula, and our more recent comments made December 3, 2009 and March 1, 2010 on the latest Expert Panel Report. IFC's expertise, experience, and review of the relevant literature leads us to conclude that the safety of soy-based infant formulas (SIF) has been adequately addressed in previous reviews and that the weight of scientific evidence in new research continues to uphold SIF safety. We do not believe the DB assessment of "possible concern" about the safety of SIF is scientifically justified. Further, we are very concerned that in going forward with this unbalanced evaluation the DB may unnecessarily alarm parents, causing them to potentially switch infant formulas or to some other food product, which could result in immediate harm to their child's nutrition and health.

* IFC members are Abbott Nutrition, Mead Johnson Nutrition, Nestlé Infant Nutrition, and Pfizer Nutrition.

Our ongoing review of the scientific evidence and our review of the January 15, 2010 Expert Panel Final Report and the DB finds that there is no new information that provides sufficient justification for generating an increased level of public concern about the overall safety of SIF. We reaffirm our position that SIF safely provide necessary and appropriate nutrition for normal growth and development in term infants. This view is consistent with that expressed more than a decade ago by the 1997 National Institutes of Health/U.S. Food and Drug Administration (FDA) Panel Meeting on the significance of phytoestrogens in SIF. It is also supported by the 2008 position of the American Academy of Pediatrics (AAP) that the use of SIF is a safe, effective alternative to provide appropriate nutrition for normal growth and development in term infants (1).

Some of the extensive evidence supporting the safe use of SIF was provided in our December 3, 2009, and March 1, 2010 comments. We remind CERHR that for almost half a century modern SIF have been fed safely to over 25 million American infants. These formulas are commonly used to achieve successful medical outcomes in infants with IgE-mediated cow milk allergy, cow milk-based formula intolerance, lactose intolerance, galactosemia, and to provide an important infant feeding alternative as a vegetarian human milk substitute, and in observance of religious and ethical practices and traditions. While there is debate in the international medical community regarding the appropriate uses of SIF, the American Academy of Pediatrics and the major international pediatric societies agree that SIF can safely provide required nutrition for normal term infants.

Specific Comments on the Draft NTP Brief on Soy Formula dated March 16, 2010

We note that, “The NTP Brief is intended to provide clear, balanced, scientifically sound information.” Yet, we believe that the DB fails to achieve these goals. In its present form the information and interpretations contained in the DB are confusing, inconsistent, and not balanced. In the text that follows, the IFC will discuss the multiple places where the DB falls short in its analysis of the issues. First, the DB consistently fails to acknowledge the low level in humans of biologically active isoflavones (aglycones) compared to rodent models, and makes inappropriate comparisons to outcomes in rodents with many-fold higher levels of the aglycone isoflavones. Second, the DB does not recognize that the absence of clinical evidence of reproductive harm of soy formula has any value, and continues to lack any analysis of history of safe use of SIF. Third, the DB assigns relevance to clinical studies that do not reach statistical significance. Finally, the entire NTP analysis ignores the vast experience with successful use of soy-based nutrition in animal agriculture, especially in swine nutrition since swine are now known to be the animal model that most closely models human isoflavone metabolism.

On page 1, the DB accurately lists the general composition of SIF, identifies the major isoflavones found in SIF: genistin, daidzin, and glycitin, and notes that these sugar-bound isoflavone forms are not hormonally active. The DB also reports that after gastrointestinal uptake 97-99% of soy isoflavones found circulating in human blood are bound, or conjugated, to another molecule, again making them hormonally *inactive*. The fact that only 1-3% of soy isoflavones in human blood are in a hormonally active form is critical to interpreting dose/response toxicity data. While the predominance of conjugated isoflavone forms in humans is acknowledged on page 2, this important finding is not generally used in the later interpretation of animal model results. This is rationally inconsistent and neither balanced nor scientifically sound.

Page 3 of the DB accurately describes SIF usage patterns. Generally, SIF are recommended to manage infant feeding problems associated with intolerance symptoms. Of infants fed SIF, less than 25% receive SIF from birth. The majority of SIF is used to manage intolerance to lactose, galactose, or cow-milk protein. SIF are also effectively used to manage infants with cow milk allergy, despite US and European Pediatric Society recommendations to the contrary (1, 2). Since these conditions usually appear some time after birth, it is common for infants to be fed human milk or cow milk-based formulas before they are switched to SIF. This is reflected in the Gilchrist (3) and Zung (4) studies and a number of other reports. This “some time after birth formula switching pattern” reflects actual soy formula usage. Patient enrollment in the Arkansas

Children's Nutrition Center Beginnings Study reflects this reality, yet the Gilchrist report from this study is criticized in the DB and many of the publications from this study were assessed as of "no utility" in the Expert Panel Report. This assessment is neither balanced or scientifically sound. The Expert Panel recommended that the Beginnings Study results would have greater value if continued recruitment did not permit such extensive dietary transitions or data are collected prior to these transitions. With either the current or the Expert Panel-recommended enrollment strategy, sub-set statistical analyses could be used to identify clinical outcomes associated with particular feeding patterns. In setting up valid animal models to evaluate the human toxicity potential of SIF, the actual human exposure patterns should guide the experimental design. For SIF, this would include feeding soy protein, genistin, daidzin, and glycitin together in a design that also assessed the effects of mixed feeding with animal milk and cow milk-based formulas.

The DB accurately describes SIF-fed infant genistein blood exposure patterns indicating a geometric mean whole blood total genistein concentration of 757 ng/mL. This value is compared to the whole blood total genistein concentration in US infants fed cow milk-based formula of 14.2 ng/mL (SIF infants 53.3X greater), and human milk-fed infants of 10.8 ng/mL (SIF infants 70.1X greater). Indicating the DB's lack of scientific balance, the text also indicates: "Average blood levels of total genistein in the soy infant formula-fed infants were ~160-times higher than the mean levels of total genistein in omnivorous adults in the United States (4.7 ng/ml)..." but fails to acknowledge that plasma genistein in SIF-fed infants is only 6.5X that of Japanese men on a traditional diet and 17.1X that of UK adult vegans. The IFC does not believe that any of these comparisons are especially useful, but in the context of a document that is intended to inform lay audiences, the lack of scientific balance is concerning for its power to mislead the public.

Page 7 of the DB asks a critical question: "Can Soy Infant Formula or its Isoflavone Contents Adversely Affect Human Development?"⁴ The DB answers "Possibly."

Footnote⁴ indicates the following possible answers to the question: "Yes, Probably, Possibly, Probably Not, No, or Unknown." We note that none of these terms are meaningful in quantitative scientific risk assessment. In considering the meaning of "Possibly" might have for general readers we note that on the scale given, this answer is as close to "Yes" as it is to "No". We believe that a substantial portion of general readers would reasonably interpret "Possibly" as a 50 – 50 chance, and that most would interpret "Possibly" as a very real and significant risk.

The use of "Possibly" as an answer to the critical question of the toxicological analysis of SIF certainly fails the goal of providing clear information, and it is not supported by the scientific evidence.

In justifying this answer the DB indicates that, "...concern has been expressed that feeding soy infant formula might adversely affect development of the reproductive system. There are presently not enough data from studies in humans to confirm or refute this possibility." This claim lacks credibility in light of the fact that in the NTP Expert Panel analysis, 52 of the ~80 human studies evaluated (65%) were judged to be of "no utility". The remaining 28 studies were designated to be of "limited utility" and none of the human studies were judged to be of "high utility." IFC reminds the BSC that the vast majority of these clinical studies were published in peer-reviewed scientific journals, all were approved by Internal Review Boards / human subject use committees, and most were funded through highly competitive grant systems. IFC questions how any clinical study involving trained medical observation of infants fed SIF in a controlled setting can be judged as providing "no utility" in assessing the developmental toxicity of SIF. We find the DB's conclusion of "insufficient evidence" unsubstantiated when the DB is based on an analysis that classifies published studies involving more than 7,600 patients as providing "no utility" in addressing human developmental toxicity. The IFC also notes that there are a number of important clinical studies in the literature that were not reviewed in the NTP analysis. We acknowledge that the "perfect clinical trial" (by today's standards) to assess the developmental toxicology of soy formula has not been reported and is not planned. Nevertheless, the current

clinical data base is robust and a claim that there is not enough clinical data to have identified significant soy formula developmental toxicity is not scientifically justified.

No clinical evidence of adverse effects on human development is mentioned on page 7. Justification for the “Possibly” answer is based on inappropriate and uncorrected animal data: “...blood levels of total genistein in infants fed soy infant formula can exceed blood levels in rats administered genistein in the diet or in mice treated by subcutaneous injection (sc injection) at dose levels that induce adverse developmental effects. Because of the high blood levels of isoflavones in infants fed soy infant formula and the lack of robust studies on the human health effects of soy infant formula, the possibility that soy infant formula may adversely affect human development cannot be dismissed.” This argument is inappropriate in that: 1. purified genistein was used in the animal experiments instead of a mixture of isoflavones and soy protein, 2. injected genistein does not effectively model oral administration, and 3. purified genistein given orally does not model the complex nature of SIF where multiple formula components and conjugated isoflavones interact in an infant isoflavone metabolism system that is not modeled by rodents. The models are uncorrected (and this is a key and recurring point) because the rodent – human comparisons are based on blood levels of total genistein. In the rodent models injected/fed genistein is found in blood mainly in the free hormonally active form, while in humans 97-99% of blood genistein is found in conjugated hormonally inactive forms. This key information described early in the DB is ignored in later analyses within the DB.

The IFC notes that there is an internal inconsistency in the paragraph: If a reasonable interpretation of “Possibly” in the context of the footnote is a “very real and significant risk, a 50 – 50 chance”, the statement: “the possibility that soy infant formula may adversely affect human development cannot be dismissed” certainly does not describe a 50 – 50 chance. IFC finds the “Yes, Probably, Possibly, Probably Not, No, or Unknown” risk assessment nomenclature confusing and scientifically meaningless, and recommends against its use. However, in the context of this highly flawed paragraph, “...cannot be dismissed” seems much closer to “Probably Not” than to “Possibly.”

We believe the text on page 7 fails, in all aspects, to achieve the goals of providing clear, balanced, scientifically sound information.

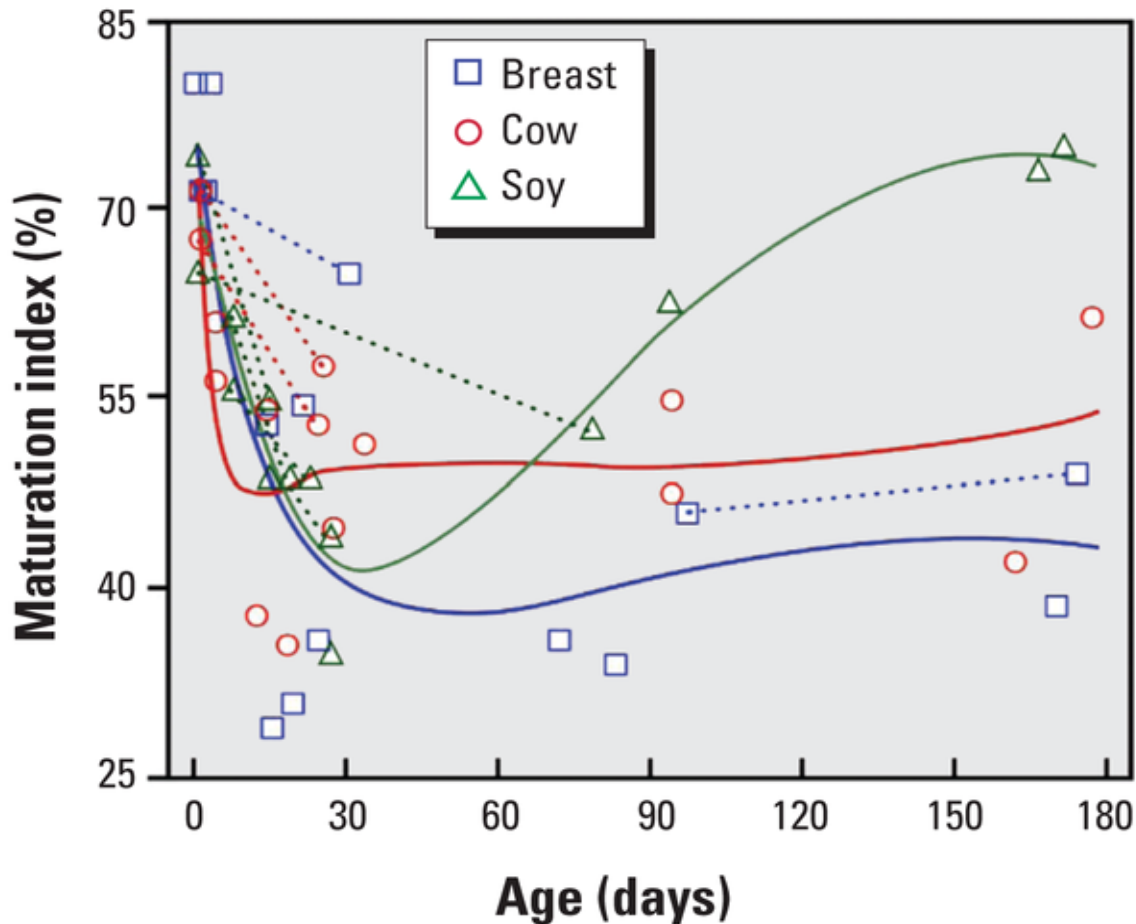
Page 9 of the DB section on “Supporting Evidence, Human Studies” begins with an assessment of Growth and Gastrointestinal Effects. The NTP, the Expert Panel, and the IFC all concur that there is sufficient evidence to conclude that the use of soy infant formula does not negatively impact growth in healthy, full-term infants. The general pediatric medical and regulatory communities view demonstration of normal infant growth as a primary indicator of the overall nutritional quality and safety of an infant formula. Many experimental formulas that seemed to be based on sound nutrition have failed this important test and were discarded. Failure to support normal growth in preterm infants is the basis for the recommendation not to feed SIF to preterm infants. The importance of achieving normal infant growth for an experimental formula is profound, yet the significance of these data seems to be missed in the NTP analysis.

Only three human studies were considered in the Expert Panel Report to have utility to assess SIF’s effects on development and subsequent function of the reproductive system. The study by Strom (5) seems most relevant because it is the only retrospective study that involves randomization of SIF and cow milk formula groups. This study involved 248 adults fed SIF and 563 fed cow milk-based formula as infants. The author’s statement of results indicates: “No statistically significant differences were observed between groups in either women or men for more than 30 outcomes. However, (in pare-wise analyses without statistical corrections for multiple comparisons) women who had been fed soy formula reported slightly longer duration of menstrual bleeding (adjusted mean difference, 0.37 days; 95% confidence interval [CI], 0.06-0.68), with no difference in severity of menstrual flow. They also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs no or mild pain, 1.77; 95% CI, 1.04-3.00).” As pointed out in the DB, these differences would not be considered statistically

significant if a multiple comparison adjustment were applied to account for the number of hypothesis. The authors conclude: “Exposure to soy formula does not appear to lead to different general health or reproductive outcomes than exposure to cow milk formula. Although the few positive findings should be explored in future studies, our findings are reassuring about the safety of infant soy formula.” The other two studies described effects on the breast and are discussed separately below.

The DB also assesses the recent report by D’Aloisio (6) that studied the association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in women enrolled in the “Sister Study.” In a troubling demonstration of lack of clarity, balance, and scientific soundness the DB describes results of this study as showing “a 25% higher early uterine fibroid diagnosis (diagnosis by the age of 35) for women who reported being fed soy formula during infancy (relative risk = 1.25, 95% confidence interval of 0.97 – 1.61) [note the lack of statistical significance with the 95% confidence interval including 1.00] (D’Aloisio et al. in press). There was also a higher risk of a similar magnitude in association with being fed soy formula within the first two months of life (adjusted RR = 1.25; 95% CI: 0.90, 1.73) [again note the lack of statistical significance with the 95% confidence interval including 1.00]. These findings were based on assessment of 19,972 non-Hispanic white women ages 35 to 59 at enrollment in the NIEHS Sister Study.” The DB fails to acknowledge the statistically significant associations with fibroids reported by D’Aloisio: DES use (adjusted RR = 1.42; 95% CI: 1.13, 1.80), Pregnancy Diabetes (adjusted RR = 2.05; 95% CI: 1.16, 3.63), and Born \geq 1 month early (adjusted RR = 1.64; 95% CI: 1.27, 2.13), or indicate that along with SIF feeding, there was no significant association between 12 other early-life exposures and uterine fibroids (D’Aloisio, Table 2).

The DB discusses the study by Bernbaum, et al. (7), in particular the data on vaginal cell maturation index: “the trajectory of maturation index appeared to differ in the infants fed soy infant formula ($p = 0.07$), such that these infants tended to have a higher maturation index at 3 to 6 months compared to infants fed breastmilk or a cow milk-based formula. Vaginal cell maturation indices are used as a measure of estrogen effects in adult women and have also been used in the diagnosis and evaluation of treatment for precocious puberty in girls.” The vaginal cell maturation index data from this section of the Bernbaum paper is shown below. Note that the DB interpretation is based on *one* data point at 3 months and *two* data points at 6 months, all from different individuals in the cross-sectional study design. IFC’s interpretation of these data is that there is no clear indication of difference among the groups.



Bernbaum, (7), Figure 2. Maturation Index (%) of vaginal wall cells versus age (days). Line segments connect observations from multiple visits by the same child at different ages.

The method for measuring vaginal cell maturation index (VCMI) is important to understand in assessing these data. Bernbaum indicates that the method has not been previously used in infants, but that it can be used in the diagnosis and evaluation of treatment for precocious puberty in girls and that the components of VCMI are usually used as a measure of estrogen effects in adult women. VCMI is calculated as the “percent superficial cells plus half of the percent intermediate cells”. To perform the test vaginal wall cells are collected “with infant recumbent, opening the infant’s legs and using a cottontipped swab to rub the introitus for 10 sec. The swab was placed in a vial of Cyto-Rich preservative and sent to a contract laboratory to be processed as a Papanicolaou smear. Slides were read by standard methods...” (7). There is no description of, or reference for, the cell grading criteria and no explanation for the logic of the VCMI calculation. The IFC questions the methods, as they seem to not be validated for infant populations and there is no discussion of method accuracy, precision, or reproducibility. Assuming that the VCMI data are real and accurate, and that there could be a difference in VCMI associated with feeding group, does that represent a positive toxic endpoint? It is clear from these same studies that the primary metabolic fate of genistein ingested by SIF-fed infants is excretion in urine. Genistein concentrations are three orders of magnitude higher in the urine of infants fed SIF compared to cow milk formula-fed infants (8). Any change in VCMI may be transient and related to the topical estrogenic effects of high concentrations of urinary genistein, with no long term toxic reproductive effects. There is no known correlation between VCMI and any clinical pathology in infants. IFC is unaware of correlations between VCMI and toxicological effects in adults.

IFC notes the description of the upcoming NIEHS-sponsored IFED study (page 12 of the DB) which will be carried out at the Children's Hospital of Philadelphia. We also realize that all of the commonly encountered clinical study design limitations described in the Expert Panel Report (non-random or unspecified method of assignment to feeding groups, the use of self-selected breast- and formula-feeding mothers, failure to control for the reasons for which soy formula was used, early and inconsistent introduction of solid foods, and lack of masking of parents and outcome assessors to formula assignment) are in fact part of the IFED study design. We do not believe that the addition of another 100 non-randomized subjects to the SIF data base justifies the cost of this study.

The IFC is concerned to again see the paper by Freni-Titulear (9) represented in the DB (page 14) as a possible indication of a linkage between SIF consumption and premature thelarche (PT), without disclosure and discussion of the later paper by Colon (10) which shows a stronger correlation between PT and significantly high levels of phthalates in the blood of 68% of PT patients compared to only 3% of matched control patients. In describing their results Freni-Titulear et al. indicate: "These statistical associations are probably not sufficient to explain the reported increase because in over 50% of the case subjects there was no exposure to any of the risk factors for which statistical associations were found." IFC has brought the Colon study report to the attention of NTP in written comments dated June 30, 2006 and March 1, 2010. The continued absence in the DB of a discussion of the 2000 Colon study as a qualifier for the Freni-Titulear paper seems purposeful and certainly fails the goal of "clear, balanced, and scientifically sound." Furthermore, at the time these cases were reported SIF from the same batches were widely distributed and there were no additional reports from other locals.

General comments on the animal data reviewed in the DB:

The DB indicates, and IFC concurs, there is sufficient evidence to conclude that high levels of genistein, by itself produce developmental toxicity in male and female mice and rat models. However, these rodent toxicities are only seen at doses substantially higher (4 - 22 fold higher in mice and 2.7 - 44 fold higher in rats) than observed for human infants fed SIF. More significantly, there are very clear physiological differences between species. In the rodent models the predominant circulating form is unconjugated genistein, which is chemically and biologically different than the inactive conjugated forms of genistein that typically circulate in humans. IFC reminds BSC of the March 1, 2006 comments on the 2006 Draft Expert Panel Report on Soy Formula made by Dr. Kenneth Setchell, Cincinnati Children's Hospital. Dr. Setchell provided compelling arguments that "much of what has been shown in immature and adult rodents (regarding soy formula safety) be disregarded as irrelevant to the human newborn and infant." We believe his analysis reflects the balance of current scientific evidence. We question how, given the significant physiological species differences in genistein metabolism documented in the literature, the NTP reached a different conclusion, specifically that "The experimental animal data are considered relevant to the assessment of human risk."

The IFC notes that many of the genistein effects seen in the animal experiments are quite profound. The DB lists accelerated vaginal opening (early onset of sexual maturation), altered estrous cyclicity, decreased body weight, decreased anogenital distance, increased time to testicular descent, decreased fertility to the point of sterility, and morphological changes in male mammary glands. All of these changes are demonstrated using relatively small populations of animals. If any of these experimental animal toxicities predicted actual human health problems, we believe that these symptoms would have been detected by the health care system in the 25 million infants fed SIF over the past 50 years.

With regard to animal models, IFC would like to reiterate some general comments made in 2006 and again in December of 2009 about the incompleteness of the animal data reviewed by NTP. After highlighting this concern in 2006, we were disappointed that the NTP's 2009 Expert Panel

did not include any agricultural experts. We remind the BSC that soy protein, in the form of soybean meal (typically with isoflavone levels far exceeding those of soy protein isolates used in human nutrition) is the major protein source in the vast majority of current American agricultural animal starter, grower, and finishing or production rations. The ultimate success of US animal production agriculture requires animal diets that support the highest levels of growth and reproductive efficiency. America produces over 103 million cattle, over 200 million hogs, 250 million turkeys, and about 2 billion broiler chickens per year (2008 USDA data). In addition there are approximately 338 million soy-fed egg laying chickens annually that contribute to the American food supply. All of these agricultural animal production industries are extremely sensitive to reproduction efficiency or other feeding-related health problems. Soy-based American agriculture is operating at record levels of efficiency and production. Yet, these enormous numbers of soy-fed animals, some of which are much better models of human physiology than isoflavone-treated rodents, were again completely ignored in the NTP's evaluation of soy "toxicity." This is of particular concern in view of the identification of the pig as the best animal model of human isoflavone metabolism (11). American farmers have been performing a pig-soy isoflavone feeding experiment more than 200 million times per year for over half a century. Given the superior similarity between human and porcine isoflavone metabolism, we again question why use of soy in commercial swine production has not been part of the SIF toxicology analysis or part of the NTP's future research plans.

Page 33 of the DB asks a second critical question: "Should Feeding Infant Soy Infant Formula Cause Concern?" Again, the DB answers "Possibly."

With the discussion of the meaning of the term "Possibly" from page 3 in mind, IFC believes that this answer also falls far short of the goal of providing clear information, and it is not supported by the scientific evidence listed on pages 33 and 34.

The most important statement of fact on page 33 of the DB regarding the feeding of SIF is: "...these types of adverse effects have not been reported in humans during 60 years of soy infant formula usage..." The IFC believes that the accuracy of this statement alone requires a "No" or "Probably not" answer. With more than 25 million infants successfully fed SIF over this time frame there is no reasonable chance that SIF could cause the kinds of serious health problems predicted by the animal data.

With no clinical indication of human toxicity, the DB turns to animal data but this discussion also lacks scientific merit. Specifically, the DB lists the median total genistein concentration of SIF-fed infants at 890 ng/mL (free genistein = 8.9 – 26.7 ng/mL) and compares these levels to mice injected with 50 mg/kg bw/day of purified free genistein to yield serum concentrations of 1,837 ng/mL (a 206 to 68.8 fold excess). Later, on pages 33 and 34, these human blood values are compared to F1 rats dosed at roughly 10 times the human SIF-fed genistein intake levels since conception. These comparisons lack any scientific veracity and do not justify the "Possibly" answer.

It is important to understand the magnitude of the unwarranted and unjustified disruption in infant feeding practices that this position by NTP may cause. A pronouncement of "possible concern" over the safety of SIF by an important Federal agency is likely to cause undue fear among parents of infants that have in the past or are currently feeding soy formulas for legitimate medical reasons. For many of these patients SIF is a cost-effective way to solve medical or feeding intolerance issues.

A confirmation of the importance of SIF in managing infant nutrition is found in a very recent report by Sladkevicius et al. (12). This study analyzes records of nutritional management and outcomes for 1,000 cow milk formula-allergic infants contained in the UK Health Improvement Network data base. Of the 1,000 infants reviewed, 60% were initially managed with SIF. Of these, only 9% were intolerant to SIF, a 91% success rate. Eighteen percent of the infants were managed with extensively hydrolyzed formula. Of these, 29% remained symptomatic, a 71%

success rate. The average cost of SIF in the study was \$7.88 / 400 gm while the cost of the extensively hydrolyzed formula was \$15.18. The superior efficacy and the lower cost of SIF probably explain its high use level in this UK population.

Need for additional research

Since IFC's June 2006 written comments on the NTP-CERHR Expert Panel Reports on the Reproductive and Developmental Toxicity of Genistein and Soy Formula, our December 8, 2006 written comments on the NTP-CERHR Draft Brief on Soy Formula and Genistein, and our December 3, 2009 written comments on the Expert Panel Draft Report, IFC has been concerned that the NTP does not include any attempt, nor does it suggest as follow-up research, to analyze history of safe use (HOSU) data. There is a vast wealth of human and animal experience that seem to meet the criteria for valid toxicological analysis of HOSU data put forward by the National Research Council Institute of Medicine (13). For example:

1. Soy formula is used in a traditional medical system.
2. Extensive HCP monitoring of infants assures clinical AEs would be detected and reported.
3. Soy formulas have been and are now ingested.
4. Current and past soy protein isolate ingredients are the same, or similar.
5. Current and traditional soy formula intakes are the same.
6. Current and traditional soy formula compositions are very similar.
7. Modern duration of use is consistent with historical pattern.
8. Modern indication for use is consistent with historical use.
9. Modern target population is similar to historical population.

HOSU analysis was proposed to NTP several times in the past, yet the strategy is not mentioned or acknowledged in the current DB. The omission is very difficult to understand, especially in the context of the DB's conclusion, "Evidence is insufficient." This raises questions about the objectivity and diversity of approaches of the NTP. An examination of the composition of the 2006 and 2009 Expert Panels shows a predominance of toxicologists and an underrepresentation of pediatric clinical experts. Also, there were no representatives from veterinary medicine, food animal nutrition, or animal agriculture on either of the Expert Panels. We note that this lack of representation for important groups was pointed out to NTP in our June 30 written comments, but that this information had no apparent influence on the selection of the 2009 Expert Panel.

The IFC supports the careful and complete examination of the safety and efficacy of all types of infant formulas. We also encourage the appropriate continued evaluation of the safety and efficacy of SIF. As in the past, we encourage NTP to consider a carefully designed HOSU study. We are fully aware of the difficulties associated with retrospective research based on personal recall, but we are confident that NTP can create useful information with such an approach. Because pigs are the best model for human isoflavone metabolism, we also encourage NTP to investigate the vast experience of the domestic swine industry with soy nutrition. The "perfect experiment" to assess SIF effects on human development would involve randomization on thousands of infants, who would then be followed for 6 decades. This is obviously not feasible given current resources and national health research priorities. The only way to get valid human data in a reasonable time period requires retrospective research.

Summary of IFC Comments and Recommendations

As indicated earlier, IFC takes very seriously all issues related to the safety and suitability of our products. Our conclusions today are essentially the same as in 2006 because the weight of scientific evidence has not changed: the general safety of soy-based infant formulas in term infants, at levels commonly consumed, has been comprehensively and unequivocally established. There is no valid clinical data (either historical or new) indicating reproductive or developmental toxicity of soy-based infant formulas. Artificial laboratory rodent and primate

animal models testing dietary components outside a food (formula) matrix, in species with isoflavone metabolism grossly different than humans, with unrealistically high doses, and by non-dietary exposure routes offer no public health benefit in the understanding of practical food toxicology, and should not be supported through continued governmental funding.

Soy-based infant formulas safely provide appropriate nutrition for normal growth and development in term infants and give parents and health care professionals an important and sometimes critical infant feeding option. If parents are unnecessarily alarmed about the safety of feeding soy infant formulas, they may choose to feed something else that is neither proven safe nor nutritious and thus is not in the best interest of their infants.

The IFC concurs with the American Academy of Pediatrics' recommendation contained in their February 26, 2010 comments to NTP, and with the independent Expert Panel vote of Dr. Jatinder Bhatia, Chair of the American Academy of Pediatrics Committee on Nutrition that the risk level regarding the possibilities that human development might be adversely affected by consumption of soy infant formula is of negligible concern.

As indicated above, IFC finds the "Yes, Probably, Possibly, Probably Not, No, or Unknown" risk assessment nomenclature confusing, misleading, and meaningless, and recommends against its use. If NTP insists on this expression of risk IFC believes that the "Probably Not" answer is much more appropriate than the "Possibly" answer. As discussed above, "Possibly" is not supported by the weight of the scientific evidence or the qualifying language used by NTP ("...cannot be dismissed" and "...not sufficient to dismiss the possibility of subtle or long-term adverse health effects").

The IFC appreciates the opportunity to comment on the 2010 Draft NTP Brief on Soy Infant Formula.

Respectfully submitted,

(Redacted)

Mardi K. Mountford, MPH
Executive Vice President

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